ACTG A5336

A Randomized Pilot Study of Ruxolitinib in Antiretroviral-Treated HIV-Infected Adults

ClinicalTrials.Gov ID: NCT02475655

Statistical Analysis Plan

Version 2.0

This is ACTG A5336 SAP Version 2.0 with names of authors, names of publication writing team members, and analysis timeline redacted.

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Table of Contents

1 Introduction

The Primary Statistical Analysis Plan (SAP) describes the proposed content for the primary statistical analysis report of ACTG A5336, which addresses the primary and secondary objectives of the study. This document also describes the primary and secondary outcome measures for which results will be posted on ClinicalTrials.gov. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study and has been developed to facilitate discussion of the statistical analysis components amongst the study team; and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary analysis report.

Analyses for the primary analysis report will be initiated once the last participant has completed the Week 12 study visit; details on the analysis timeline are located in **Appendix 1**. In addition, all primary and secondary outcomes outlined in this SAP will be submitted to ClinicalTrials.gov within 1 year of the PCD (5 weeks after the last participant enrolls).

Additional specifications and details on other key elements of the primary analysis report are provided in the Analysis Implementation Plan (AIP) in **Appendix 2**.

1.1 Key Updates to the SAP

The SAP was updated after the final interim review, but prior to the final analysis, to include the following changes:

- Reformat to be compliant with new SOP requirements
- Remove details on interim analyses
- Update the statistical test for safety from a Fisher's exact test to a mid-p Fisher's exact test, which is a less conservative test, therefore more appropriate to compare safety

2 Study Overview

2.1 Design

A5336 is a multi-center, randomized, open-label, two-arm, phase IIa study. Eligible participants on approved ART with virologic suppression will be randomized to receive ruxolitinib or no study treatment to measure safety and tolerability and to determine whether there are changes in systemic immune activation and inflammation after 5 weeks of treatment with ruxolitinib.

A total of 60 participants will be randomized 2:1 to ruxolitinib or no study treatment; 40 on ruxolitinib and 20 on no study treatment. The study aims to enroll at least 15 participants on efavirenz (EFV) in order to have at least 8 ruxolitinib-treated participants to evaluate pharmacokinetic (PK) interactions with EFV.

The study population consists of HIV-1 infected males and females ≥ 18 and < 75 years of age on stable ART for at least 12 weeks prior to study entry containing TDF/FTC, TAF/FTC, TDF/3TC, or ABC/3TC, plus a NNRTI or INSTI (not containing cobicistat) who:

- Are on ART for at least 2 years
- Have virologic suppression (see protocol for definition)
- Have CD4+ T cell count > 350 cells/mm^3 within 45 days prior to study entry
- Have no medical conditions, or concomitant medications, prohibiting the use of janus activating kinase-signal transducer and activator of transcription (Jak-STAT) inhibitor

All participants will be followed for up to 12 weeks after randomization. Participants randomized to the ruxolitinib arm will receive 10 mg of ruxolitinib orally twice daily for 5 weeks and then will be followed off-treatment for an additional 7 weeks.

2.2 Hypotheses

1) The use of ruxolitinib for 5 weeks with antiretroviral therapy (ART) consisting of: tenofovir/emtricitabine (TDF/FTC) or abacavir /lamivudine (ABC/3TC) + a nonnucleoside reverse transcriptase inhibitor or integrase strand transfer inhibitor (NNRTI or INSTI) will be safe for virologically suppressed participants.

2) The use of ruxolitinib for 5 weeks with ART will be tolerable for virologically suppressed participants.

3) The use of ruxolitinib for 5 weeks with ART for virologically suppressed participants will reduce systemic immune activation and inflammation.

2.3 Objectives

The Primary SAP addresses the following primary and secondary objectives listed in the study protocol. The secondary PK objectives will be analyzed outside of SDAC and their analyses will be outlined in a separate SAP.

2.3.1 Primary Objectives

1) To evaluate the safety of ruxolitinib in ART-treated HIV-1 infected virologically suppressed participants during 5 weeks of treatment [Protocol Objective 1.2.1].

2) To evaluate the tolerability of ruxolitinib in ART-treated HIV-1 infected virologically suppressed participants during 5 weeks of treatment [Protocol Objective 1.2.2].

3) To compare changes in interleukin-6 (IL-6) levels between baseline and week 5 in ART-treated HIV-1 infected virologically suppressed participants who are randomized to ruxolitinib and those randomized to receive no study treatment [Protocol Objective 1.2.3].

2.3.2 Secondary Objectives

1) To evaluate the safety of ruxolitinib in ART-treated HIV-1 infected virologically suppressed participants during all on-study visits through week 12 [Protocol Objective 1.3.1].

2) To compare changes in IL-6 levels between baseline and week 12 in ART-treated HIV-1 virologically suppressed participants who are randomized to ruxolitinib to changes in those participants randomized to receive no study treatment [Protocol Objective 1.3.2].

3) To assess whether the use of ruxolitinib will decrease levels of other measures of inflammation and immune activation including sCD14, tumor necrosis factor alpha (TNF-α), IL-1α, IL-1β, IL-18, macrophage colony stimulating factor (mCSF), neopterin, HLA-DR, CD38, and both the distribution of monocyte subsets (defined by expression of CD14+ and CD16+) and phenotypic indices of their activation during 5 weeks of treatment and at week 12 [Protocol Objective 1.3.3].

4) To examine whether the use of ruxolitinib is associated with changes in HIV-1 plasma viral load levels (by a commercial clinical assay and single-copy assay) and CD4+ T cell counts in HIV-1 infected participants at baseline compared to 12 weeks after initiation of treatment for those receiving 5 weeks of ruxolitinib versus those receiving no study treatment [Protocol Objective 1.3.4].

5) To assess changes from baseline in the HIV-1 reservoir, specifically plasma HIV-1 RNA by single copy assay (as above), cellular HIV-1 RNA and total DNA, 2 long-terminal repeat sequences [LTRs], and integrated DNA [Protocol Objective 1.3.5].

6) To evaluate whether the use of ruxolitinib is associated with more frequent reactivation of human herpes viruses (ie, cytomegalovirus [CMV], Epstein Barr virus [EBV], herpes simplex viruses [HSV], human herpes viruses [HHV] 6, 7, and 8) as measured in longitudinally collected oral swabs [Protocol Objective 1.3.7].

2.4 Outcome measures

2.4.1 Primary Outcome Measures

Safety

1) Proportion of participants on the *Ruxolitinib arm* who experience any of the following safety milestones while on-treatment:
   - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
   - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
   - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
   - New or recurrent CDC category C AIDS-indicator condition.
   - HIV-1 associated infection including Herpes zoster.
   - Lymphoproliferative malignancies.
   - Discontinuation of ruxolitinib due to thrombocytopenia.
   - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
   - Any Grade 4 or recurrence of Grade 3 toxicity related to study drug.
   - New diagnosis of pneumonia, sepsis, or bacteremia.

2) Proportion of participants who experience any of the following safety milestones on-study from entry through week 5 by study arm:
   - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
   - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
   - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
   - New or recurrent CDC category C AIDS-indicator condition.
   - HIV-1 associated infection including Herpes zoster.
   - Lymphoproliferative malignancies.
   - Occurrence of Grade 2 or higher thrombocytopenia.
   - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
   - Any Grade 4 or recurrence of Grade 3 toxicity.
   - New diagnosis of pneumonia, sepsis, or bacteremia.

3) Proportion of *each* of the following components that occurred on-study from entry to week 5 by study arm:
    - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
    - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
    - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
    - New or recurrent CDC category C AIDS-indicator condition.
    - HIV-1 associated infection including Herpes zoster.
    - Lymphoproliferative malignancies.
    - Occurrence of Grade 2 or higher thrombocytopenia.
    - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
    - Any Grade 4 or recurrence of Grade 3 toxicity.
    - New diagnosis of pneumonia, sepsis, or bacteremia.

Tolerability

4) Occurrence of premature discontinuation of study treatment, including reasons for discontinuations.

Efficacy

5) Participant-specific change in log10-transformed plasma IL-6 (using geometric means of two ELISA measurements at pre-entry and entry, and weeks 4 and 5).

2.4.2 Secondary Outcome Measures

1) Proportion of participants on Ruxolitinib who experienced any of the following safety milestones during study follow-up from entry through week 12.
    - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
    - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
    - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
    - New or recurrent CDC category C AIDS-indicator condition.
    - HIV-1 associated infection including Herpes zoster.
    - Lymphoproliferative malignancies.
    - Discontinuation of ruxolitinib due to thrombocytopenia.
    - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
    - Any Grade 4 or recurrence of Grade 3 toxicity related to study drug.
    - New diagnosis of pneumonia, sepsis, or bacteremia.

2) Proportion of participants who experienced any of the following safety milestones during study follow-up from entry through week 12 by study arm:
    - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
    - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
    - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
    - New or recurrent CDC category C AIDS-indicator condition.
    - HIV-1 associated infection including Herpes zoster.
    - Lymphoproliferative malignancies.
    - Occurrence of Grade 2 or higher thrombocytopenia.
    - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
    - Any Grade 4 or recurrence of Grade 3 toxicity.
    - New diagnosis of pneumonia, sepsis, or bacteremia.

3) Proportion of *each* of the following components that occurred during study follow-up from entry to week 12 by study arm:
    - For participants with entry CD4+ T cell count < 700 cells/mm^3, confirmed CD4+ decline > 33% of baseline and to < 350 cells/mm^3.
    - For participants with entry CD4+ T cell count ≥ 700 cells/mm^3, a confirmed CD4+ T cell decline > 50 % of baseline.
    - Confirmed HIV-1 RNA level above the lower limit of quantification in the absence of an interruption in ART.
    - New or recurrent CDC category C AIDS-indicator condition.
    - HIV-1 associated infection including Herpes zoster.
    - Lymphoproliferative malignancies.
    - Occurrence of Grade 2 or higher thrombocytopenia.
    - Grade 4 or recurrence of Grade 3 anemia/neutropenia.
    - Any Grade 4 or recurrence of Grade 3 toxicity.
    - New diagnosis of pneumonia, sepsis, or bacteremia.

4) Occurrence of protocol-defined reportable adverse events (all diagnoses, Grade 3 or higher sign/symptoms or laboratory values, any signs/symptoms or laboratory values that led to a change in treatment or met ICH, EAE, or SAE guidelines) at any post-entry time point.

5) Safety Laboratory values (estimated creatinine clearance, creatinine, AST (SGOT), ALT (SGPT), ANC, hemoglobin, platelet count) across all study weeks (at entry, week 1, and week 2, and arithmetic means at weeks 4 and 5, and at weeks 10 and 12).

6) Change in safety laboratory values (estimated creatinine clearance, creatinine, AST (SGOT), ALT (SGPT), ANC, hemoglobin, and platelet count) across all study weeks (at weeks 1 and 2, and arithmetic means at weeks 4 and 5 and at weeks 10 and 12).

7) Change in log10-transformed plasma IL-6 across all study weeks (geometric means of pre-entry and entry, and week 10 and 12).

8) Changes in soluble markers of immune activation and inflammation in the peripheral blood (sCD14, TNF-α, IL-1α, IL-1β, IL-7, IL-10, IP-10, IL-18, mCSF, and neopterin) across study weeks from baseline (geometric mean of pre-entry and entry) to week 4/5 (geometric mean of week 4 and week 5) and week 12.

9) Changes in cellular markers of immune activation and inflammation in the peripheral blood (HLA-DR, CD25, CD38, CD69, CD127, Ki67, BCL2, a4b7, CX3CR1, PAR-1 measured on CD4 and CD8 cells; monocyte subsets (classical, inflammatory, and patrolling) defined by CD14 and CD16 expression; proportion of monocyte subsets (classical, inflammatory, and patrolling) expressing CCR2, CX3CR1, and CD163) from entry to weeks 5 and 12.

10) Level of plasma HIV-1 RNA at baseline and weeks 2, 5, and 12.

11) Change in CD4+ T cell counts from baseline (mean of pre-entry and entry) to weeks 2, 5, and 12.

12) Changes in HIV-1 reservoir (HIV-1 RNA by SCA, cellular HIV-1 total RNA and DNA) from entry to weeks 5 and 12.

13) Level of CMV shedding at pre-entry, entry, and weeks 1, 2, 4, 5, 10, and 12.

2.4.3 Other Outcome Measures

1) Changes in HIV-1 reservoir (2 long-terminal repeat sequences [LTRs], and integrated DNA) from entry to weeks 5 and 12.

2) Level of EBV, HSV, HHV-6, HHV-7, and HHV-8 shedding at pre-entry, entry, and weeks 1, 2, 4, 5, 10, and 12.

3 General Analysis Considerations

Study entry is defined as the date of the entry visit recorded on study initiation case report form.

The protocol-defined study week windows are modified for analysis purposes. For all analyses, the following window definitions will be used:

Pre-entry:	The last visit that occurred at least 24 hours prior to entry, but not more than 7 days before
Entry:	The visit after randomization, and prior to initiation of study treatment: Days [0-3]
Week 1:	The first visit in the window: Days [4, 22]
Week 2:	The second visit in the window: Days [4, 22]
Week 4:	The first visit in the window: Days [25, 39]
Week 5:	The second visit in the window: Days [25, 39]
Week 10:	The first visit in the window: Days [56, 93]
Week 12:	The second visit in the window: Days [56, 93]

Baseline values are the average of pre-entry and entry values, the week 4/5 values are the average of week 4 and week 5 values, and the week 10/12 values are the average of week 10

and 12 values; averages will be calculated using geometric means for log-transformed data and arithmetic mean for non-transformed data. If missing one of the pre-entry or entry values, then the available measure will be used as the baseline value, and similarly, if missing one of the week 4 or week 5 values or week 10 or week 12 values, then the available measure will be used as the week 4/5 value or week 10/12 value, respectively.

Analyses will be done among those in the as-treated population or among those in the safety analysis population (Cameron 2008), depending on the outcome; see the Statistical Methods section for details on populations for specific outcomes. The safety analysis population will consist of all participants randomized to the no-treatment arm and all participants who took at least one dose of ruxolitinib among those randomized to the ruxolitinib arm. The as-treated population is defined as participants who meet the following conditions: (1) have data at baseline and week 4/5, (2) for the ruxolitinib arm, remained on study treatment through week 4/5 and missed no more than 6 doses cumulatively, (3) did not change ART, use prohibited medications, or had confirmed virologic failure in this time period. Participants found to be ineligible after enrollment will be included in all safety analyses, but excluded from other analyses.

Confirmed virologic failure is defined as the occurrence of two sequential plasma HIV-1 RNA values above the lower limit of quantification in the absence of an interruption of ART; the confirmatory HIV-1 RNA should occur within 7 days of receipt of the results for the first test. In the event that a suspected virologic failure is not confirmed with a follow-up HIV-1 RNA test (i.e., there is no subsequent HIV-1 RNA available), this suspected virologic failure will be considered a *confirmed* virologic failure. Confirmed CD4 count decline is defined as two sequential CD4 counts meeting the respective criteria in the absence of an interruption in ART. Adverse events are classified as related (definitely, probably, possibly) or not related (probably not, not) by site investigators.

Biomarker data distributions will be assessed for normality, and any non-normal data will be log-transformed to the log-10 scale for analysis; it is anticipated that all soluble markers will be log-transformed. Descriptive summaries of continuous baseline characteristics will include frequency, frequency missing, mean, sd, median, IQR, 10^{th} and 90^{th} percentiles, and min/max; descriptive summaries of other continuous variables will use mean and sd, or median and IQR depending upon the corresponding analysis method. The frequency and percentage will be used for all categorical variables.

4 Statistical Methods

4.1 Primary Outcome Measures

4.1.1 Safety

Tabular summaries of all primary safety outcomes will be provided for primary outcomes (1), (2), and (3), which will include frequencies and percentages overall and by study arm. Formal comparisons between study arms will contrast the proportion of participants who experienced any safety milestones on study from entry through week 5 as defined in primary outcome (2) using a one-sided mid-p Fisher's exact test with 5% type-I error.

All safety summaries will be done in the safety analysis population.

4.1.2 Tolerability

All tolerability summaries will be done in the safety analysis population.

Participant-level listings of occurrences of premature discontinuation of study treatment will be provided, including reasons for discontinuation. If a given reason for premature discontinuation occurs in more than 5 participants, then tabular summaries including frequency and percentages will also be provided. This summary will only be provided for those in the Ruxolitinib arm.

4.1.3 Efficacy

The primary efficacy analyses will be done in the as-treated population.

Analyses addressing efficacy of ruxolitinib will contrast IL-6 changes from baseline to week 4/5 between study arms. Baseline and week 4/5 are defined based on the criteria mentioned in the General Analysis Considerations section and IL-6 will be transformed to the log-10 scale for all analyses.

Formal study arm comparisons will contrast the mean change from baseline to week 4/5 between study arms. The mean and 90% confidence interval (CI) for the mean change will be calculated; corresponding p-value based on a two-sided t-test with 10% alpha will also be calculated.

Descriptive summaries of levels of IL-6 at baseline and week 4/5 will be presented by study arm using continuous summary statistics and longitudinal plots. Changes in IL-6 (log10) from baseline to week 4/5 will be summarized with the mean and a 95% CI for the change separately within each study arm; change will be presented as absolute mean log10 change and corresponding geometric mean fold-change.

4.2 Secondary Outcome Measures

4.2.1 Safety

All summaries of secondary safety outcomes will be done in the safety analysis population.

In a similar manner to the primary safety analyses, tabular summaries will be provided for secondary outcomes (1-4), which will include frequencies and percentages overall and by study arm. Formal comparisons between study arms will contrast the proportion of participants who experienced any safety milestones on study from entry through week 12 as defined in secondary outcome (2) using a one-sided mid-p Fisher's exact test with 5% type-I error.

Levels and changes in safety laboratories (secondary outcomes 5 and 6) will be summarized with continuous descriptive summary statistics. Changes in safety labs will be formally compared at week 4/5 and week 10/12 via two-sided t-tests with 10% alpha and corresponding 90% confidence intervals.

4.2.2 Longitudinal Summaries of CD4 Count and plasma HIV-1 RNA

Descriptive longitudinal summaries of levels and changes in CD4 cell counts and CD4 % will be provided by study arm and week. Formal comparisons between study arms of change from baseline will occur at all post-entry visits (week 2, 5, and 12); two-sided t-tests with 10% alpha will contrast differences between groups. In addition, change from week 5 (end of treatment) to week 12 (end of study) will also be examined. Participant narratives will be provided for those who had a protocol defined drop in CD4 cell counts (see primary safety endpoint).

Tabular summaries of categorized HIV-1 RNA levels (secondary outcome 10) by study week and arm will also be provided; no statistical inference will be done. HIV-1 RNA levels will be categorized as below or above the lower limit of quantification. Participant narratives will be provided for those who had any viral loads above the lower limit of quantification while on study.

All summaries will be done in the safety analysis and as-treated populations.

4.2.3 Immune Activation and Inflammation

The immunology markers outlined in secondary outcome measures (7-9) will be addressed in the following manner. All analyses will be done in the as-treated population, and geometric means will be used to average pre-entry and entry, week 4 and 5, and week 10 and 12, as available. As mentioned in the General Analysis Consideration section, biomarkers will be log-10 transformed as appropriate.

Descriptive summaries of levels and changes (absolute changes and corresponding fold-changes) will be done using continuous summary statistics and longitudinal plots by study week and arm. Treatment group comparisons will contrast the change from baseline at each post-entry study week using two sided t-tests with 10% alpha; corresponding p-values and 90% CIs will also be calculated. In addition, change from end of treatment to end of study will also be examined in a similar manner. Results for log-10 transformed markers will be back transformed to fold-changes for presentation as appropriate.

4.2.4 HIV-1 Reservoir

Tabular summaries of categorized HIV-1 RNA by iSCA (secondary outcome 12) will be provided by study week and arm. To compare changes in iSCA over time and between study arms, a GEE model for binary data will be used since it is anticipated that a substantial proportion of the data will be below assay limit (Riddler 2016).

Total HIV-1 DNA and cell-associated HIV-1 RNA will be log-10 transformed and summarized by arm and across study weeks with continuous summary statistics and longitudinal plots, imputing values below the assay limit as the lower limit of the assay; as with the immunology markers, results will be back-transformed to fold-changes for presentation. Total HIV-1 DNA and cell-associated HIV-RNA will also be summarized categorically as the frequency and percent below or above the lower limit; if there are differential assay lower limits, an analytic lower limit will be applied for this summary.

Results below assay limit are not anticipated for total HIV-1 DNA (Gandhi 2017). Changes from baseline will be contrasted between study arms using a two-sided t-test with 10% alpha at each visit (week 5 and week 12); in addition, a comparison between week 5 (end of treatment) and week 12 (end of study) will also be done.

Modest amounts of below assay limit observations are anticipated for cell-associated HIV-1 RNA (Gandhi 2017). To contrast changes over time between study arms, a longitudinal censored normal model approach will be used, which was developed for below assay limit HIV virology data and can handle different assay limits (Riddler 2016, Vaida 2009).

In the event that a large proportion of participants have values below assay limits for total HIV-1 DNA and cell-associated HIV-1 RNA, a binary analysis approach similar to the analysis of iSCA will be used.

All analyses will occur in the as-treated population. For GEE and longitudinal censored normal models, the analysis will also be restricted to those who have results for corresponding time points of interest.

4.2.5 CMV Co-Infection

Level of CMV shedding (secondary outcome 13), will be summarized by study week and arm as the frequency and percentage of those above and below the assay limit of detection. The proportion of participants with detectable CMV at any on-treatment time point (ever shedding at weeks 1, 2, 4, or 5) and any post-treatment time point (ever shedding at weeks 10 or 12) will be contrasted between study arms via using a two-sided mid-p Fisher's exact test with 10% type-I error.

This analysis will include all participants with available specimen.

5 Key Report Elements

In addition to the previously mentioned primary and secondary analyses, the following elements will be included in the final analysis report:

- CONSORT diagram
- Description of ineligible enrollments
- Screen failure rates with reasons
- Accrual by month, site, and stratification factors
- Baseline Characteristics
- Study/Treatment Status
- Duration of Follow-up
- ARV Regimen Status
- ART Adherence
- Concomitant Medication Use
- Additional safety summaries including EAEs, SAEs, deaths, and pregnancies

Detailed descriptions of these elements are provided in the AIP in **Appendix 2**.

6 Core Manuscript Writing Team

Redacted.

7 Citations

1. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Gruszfeld A, Kaufman B, Crown J, Chan A. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast cancer research and treatment. 2008 Dec 1;112(3):533-43.

2. Riddler SA, Aga E, Bosch RJ, Bastow B, Bedison M, Vagratian D, Vaida F, Eron JJ, Gandhi RT, Mellors JW, ACTG A5276s Protocol Team. Continued Slow Decay of the Residual Plasma Viremia Level in HIV-1–Infected Adults Receiving Long-term Antiretroviral Therapy. The Journal of infectious diseases. 2015 Sep 2;213(4):556-60.

3. Gandhi RT, McMahon DK, Bosch RJ, Lalama CM, Cyktor JC, Macatangay BJ, Rinaldo CR, Riddler SA, Hogg E, Godfrey C, Collier AC. Levels of HIV-1 persistence on antiretroviral therapy are not associated with markers of inflammation or activation. PLoS pathogens. 2017 Apr 20;13(4):e1006285.

4. Vaida F, Liu L. Fast implementation for normal mixed effects models with censored response. Journal of Computational and Graphical Statistics. 2009 Jan 1;18(4):797-817.

Appendix 1: Analysis Timeline

Redacted.

Appendix 2: Analysis Implementation Plan (AIP)

Redacted.